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Editorial

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Do changes in brain sodium channels cause central pain?

Mitchell B. Max, MD; and Neil A. Hagen, MD, FRCPC

An estimated 200,000 Americans have "central pain"—chronic pain associated with lesions of the brain or spinal cord. Central pain often accompanies lesions that include any portion of the spinothalamocortical pain pathways mediating pain and temperature[1] and has been refractory to treatment. A single randomized trial suggesting that amitriptyline reduces poststroke pain[2] appeared more than a decade ago. Two recent clinical trials in central pain expand the therapeutic options. A placebo-controlled crossover study of lamotrigine in 31 patients with poststroke pain showed a modest but significant reduction in pain,[3] and, in this issue of *Neurology,* Attal et al.[4] report that in 10 patients with spinal cord injury and 6 patients with poststroke pain, acute infusion of lidocaine transiently reduced spontaneous pain, pain evoked by light touch, and tingling.

Attal et al. point out that lidocaine's well-known effect of reducing ectopic discharge mediated by voltage-gated sodium channels in injured peripheral afferents is not relevant here, because their patients' lesions were in the CNS. They speculate that lidocaine's central analgesic action might be related to glycine, NMDA, or neurokinin receptors. However, we note that the three drugs that reduce central pain—amitriptyline, lamotrigine, and lidocaine—all block sodium channels, and speculate that central pain states may be mediated by sodium channel–related ectopic discharge from chronically injured neurons in the spinothalamocortical pathways. We are unaware of studies of sodium channel expression in humans or animal models of central neuropathic pain, but two- to fourfold increases in the number of sodium channels have been found in the demyelinated brain lesions of human MS and in demyelinated central axons of rodents.[5]

Treatment of chronic pain with currently available sodium channel blockers is limited by several considerations. The available drugs block sodium channels in heart, brain, and peripheral nerve, causing adverse effects at each site, including proarrhythmic effects in patients with coronary disease,[6] cognitive impairment, dizziness, nausea, and diarrhea. Because lidocaine is not orally bioavailable, the acute lidocaine responders in the Attal et al. study were treated with mexiletine, an orally available sodium channel blocker; none could tolerate the adverse effects. Interim results from a randomized trial[7] suggest that chronic opioid treatment reduces central pain and may be an alternative for patients in whom mexiletine, tricyclic antidepressants, or lamotrigine are contraindicated or ineffective.

More selective blockers of CNS sodium channels may improve on the modest effect reported by Attal et al. At least eight distinct subtypes of voltage-gated sodium channels have been cloned and have markedly different distributions in heart, brain, and

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From the Pain and Neurosensory Mechanisms Branch (Dr. Max), National Institute of Dental and Craniofacial Research, National Institutes of Health, Bethesda, MD; and the Tom Baker Cancer Centre and the Departments of Oncology, Clinical Neurosciences and Medicine (Dr. Hagen), University of Calgary, Canada.

Address correspondence and reprint requests to Dr. Mitchell Max, National Institutes of Health, Building 10, 3C-405, Bethesda, MD 20892-1258; e-mail: mm77k@nih.gov

nerve.[8,9] Because peripheral neuropathic pain is more common than central pain and has appeared to be more sensitive to IV lidocaine,[10] pain researchers and the pharmaceutical industry have focused on PN1, SNS/PN3, and NaN/SNS2, subtypes whose expression is largely restricted to small-diameter peripheral neurons.[9] One might also examine the changes in expression of brain-specific sodium channel subtypes in rat models of central pain and in human autopsy material, and test the effects of specific blockers when they become available. Because lidocaine binds with highest affinity to the cardiac sodium channel isoform H1, and because the site bound by local anesthetic-like drugs has been closely conserved across most of the cloned sodium channel receptor subtypes, drugs that bind differentially to sites other than the local anesthetic site may be needed.[8]

Attal et al.[4] reported that lidocaine infusion reduced pain induced by light touch ("mechanical allodynia") as well as ameliorating spontaneous pain. Extensive studies of mechanical allodynia associated with peripheral inflammation or nerve injury have shown sensitization of primary afferents or spinal wide-dynamic range projection neurons to be important mechanisms. Most patients in the current study had lesions above the spinal cord level corresponding to their symptoms, however. Therefore, the central portions of pathways activated by light touch must be investigated to understand the mechanism of this lidocaine effect.

Although thoughtful and methodologically sound, the study by Attal et al.[4] has limitations. They studied only 16 patients, and these patients had a variety of spinal cord and cerebral lesions. Patients were concurrently treated with a variety of centrally acting drugs that could interact with lidocaine and cloud the results. A large proportion of patients experienced lidocaine-related toxicity, which can have the effect of unblinding the active treatment arm. Despite these limitations, the Attal study suggests that sodium channel blockers reduce central neuropathic pain and encourages further study of the role of CNS sodium channels and their antagonists in central pain.

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